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Impact of diabetes, the diabetes duration and glycemic control on cognitive functions. A quantitative meta-analysis.

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Abstract

Patients with diabetes are a high-risk group for cognitive disorders, the exact pattern and the magnitude of this are still unclear. The research to identify the studies was performed in the databases Medline, Pubmed, ScienceDirect. Following the analysis of eligibility a number of 9 studies were included in the meta-analysis. Adults with diabetes showed lower performance than control subjects in all cognitive domains. Although the effect sizes of the diabetes on cognitive functions generally oscillate between low and moderate values they should still be considered because they can affect daily activities.

Keywords: diabetes; cognitive functions; IQ, memory; learning; attention; executive functions; visual processing; psychomotor activity

1. Introduction

Several chronic diseases, such as diabetes, a series of cardiovascular diseases and high blood pressure, are considered to be factors of major risk for the decline of intellectual abilities (Attree et al., 2003). A multitude of studies reported negative impact of diabetes on cognitive abilities, the patients with diabetes mellitus presenting a high risk factor for the development of cognitive problems compared to healthy persons (Ebady et al., 2008; Kodl & Seaquist, 2008). Although a special attention was given in the related literature to the risk of cognitive disorders

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among individuals with diabetes, the studies revealed mixed results. While some studies have suggested that diabetes is associated with a decreased performance on cognitive tests (Wu et al., 2003; Van Harten et al., 2007), others found no significant correlation between these conditions and cognitive disorder (Lindeman et al., 2001; Kumari et al., 2005). Overall, transversal studies have produced inconsistent results, often with a high degree of ambiguity; this may be attributed to discrepancies between the methods of measurement (Desrocher & Rovet, 2004). The relation between diabetes and cognitive functions is not yet clearly documented (Pasquier, 2010). We performed a meta-analysis of the relevant literature to determine the magnitude of cognitive dysfunctions in adults with diabetes compared to non-diabetic control subjects. We also propose to identify the role of the glycemic control and the diabetes duration in the impairment of cognitive processes.

2. Method

Selection of studies

The research to identify the studies on cognitive performances in patients with diabetes compared with non-diabetic control subjects was performed in the databases Medline, Pubmed, ScienceDirect using the search phrases: cognitive functions, memory, attention, learning, information processing and intelligence. They were combined with terms diabetes, type 1 and type 2 diabetes. Abstracts (989) were examined to determine if the studies meet the following inclusion criteria: 1) published or available in English 2) subjects aged between 18 and 65 (mean) 3) had a defined control group (healthy subjects), 4) studies provide sufficient information on the characteristics of participants, methodological features and the conceptualization of factors, 5) evaluated cognitive performance using standard neuropsychological tests at normal blood glucose values, 6) test results were presented for experimental and control groups. A number of 9 studies were included in the meta-analysis.

Encoding the studies

Encoding general characteristics of the studies was direct, based on information found in the study (Table 1).

Table 1. Characteristics of the studies

	Author / year	Study type	n (diabetes/ control)	Age (diabetes/ control)	Type of diabetes	Diabetes duration (Years)	Glycemic control (HbA1c)	Cognitive domains measured
1	Ryan et al. (1993)	CS	142/100	33.5±5,6/ 34.1±6.7	type 1	24.8±6.1	10.6±1.8	VeI, A,L,PV,APM, FE
2	Ryan et al. (2000)	CS	50/50	50.8±7.7/ 50.5±7.4	type 2	8.1±5.9	10.2±2.4	VeI,ViI,VeD, ViD, GM,A, PV,APM,FE
3	Cosway et al. (2001)	CS	38/38	57.7(10.3)/ 55.9(11.2)	type 2	6.0(3.0,11.3)	7.6(6.6,9.5)	IQ, VeI,ViI, VeD, ViD, GM, L,
4	Asimakopoulou et al. (2002)	CS	33/33	62.40(9.62)/ 62.40(9.62	type 2	9(5.91)	ND	WM, Vei, VeD,A, FE
5	Lobnig et al. (2005)	CS	13/13	41.3±1.3/ 38.5±1.5	type 1	27.7(14 -36)	8.2±0.3	WM, VeI, VeD, A, FE
6	Gold et al. (2007)	CS	23/23	59.2±8.4/ 59.9±8.6	type 2	6.0±6.3	6.9±0.8	WM, VeI, VeD, GM, A, FE
7	Bruehl et al. (2007)	CS	30/30	59.16±8.58/ 59.12±8,40	type 2	7.43±7.26	7.5±1.45	IQ, WM, VeI, VeD, GM, A, L, FE
8	Weinger et al. (2008)	CS	114/58	32±4/ 30±5	type 1	20±4	7.8±1.4	WM; VeI, VeD,A,L,PV,APM,FE
9	Bruehl et al. (2009)	CS	41/47	59.05±8.38/ 60.02±7.96	type 2	7±6.4	7.88±1.83	IQ,VeI, VeD

CS- cross sectional, ND- not defined, *IQ*- intelligence quotient, WM-Working memory,VeI-Verbal learning and immediate memory, ViI- Visual learning and immediate memory, VeD-Verbal delayed memory and learning, ViD- Visual delayed memory and learning, GM-Genereal learning and memory, A-Attention, *L-Language, PV-Visual processing, APM*-Psychomotor activity , *FE- Executive functions*

Cognitive functions measured in this meta-analysis were classified on the basis of the American Academy of Neurology (1996) and after the book of Lezak (2004) and other relevant classifications in the field (Strauss et al., 2006; Groth-Marnat, 2009). In the studies various tests were used to evaluate similar aspects of cognition, or the same test was used to evaluate different areas, therefore we reclassified the tests used in the studies included in the meta-analysis according to the relevance of the classification (Table 2).

Table 2. Classification of cognitive functions and tests

Cognitive domains		Examples of tests
1. Global cognitive function, IQ		(WAIS, Raven ,WASI)
2. Memory and learning		(WMS-R, WMS III; RAVLT, CVLT)
3. Working memory		Digit span (WMS R, WAIS) or other alternatives (Guild Memory Scale, Nuernberger Alters Inventar); Letter Number Sequencing scaled (WMS III)
Short-term memory	4 . Immediate verbal memory	Logical memory immediate recall subscale (WMS-R); Verbal paired associate immediate recall (WMS-R, WMS, WMS III) or other alternatives (Verbal paired associate learning test, Guild memory test, Nuernberger Alters Inventar; CVLT - short delay recall)
	5. Immediate visual memory	Visual paired associate immediate recall subscale (WMS-R, WMS, WMS III); or other alternatives (Symbol digit paired associeta learning test)
Long-term memory	6. Delayed verbal memory	Logical memory delayed recall subscale (WMS-R); Verbal paired associate delayed (WMS-R, WMS, WMS III) or other alternatives (Verbal paired associate learning test , Guild memory test, Nuernberger Alters Inventar, CVLT -long delay recall)
	7. Delayed visual memory	Visual paired associate delayed recall (WMS-R, WMS, WMS III) or other alternatives (Symbol digit paired associeta learning test)
8. Attention		Digit symbol (WAIS, WMS); Trail Making A test; Digit vigilance test
9. Language		Verbal Fluency Test;Word fluency - Controlled Oral Word Association (FAS) Test; Vocabular subscales of WASI, WAIS-R
10. Procesare vizuală/ vizuospatială		Block design (WAIS, WASI); Object assembly subtest (WAIS R)
11. Psychomotor activity		Grooved Pegboard; Embedded figures test
12. Executive functions		(STROOP test; Trail Making B test; Category test; Wisconsin Card Sorting Test; D-KEFS

Tests measuring the same cognitive domains were taken together in the analysis. Cognitive functions that could not be classified according to these areas were not included in the meta-analysis.

Statistical analysis

We computed the effect size (Cohen's d) according to the basic standard literature (Hunter & Schmidt, 2004). The results were evaluated on the same basis, following the effect size measures described by Cohen (0.2-0.5 = small, 0.5-0.8 = medium, 0.8< = large effect size) (Cohen, 1988). Data analysis was performed by the Meta-Analysis Calculator (http://www.lyonsmorris.com), complemented with custom written formulas. The first computations resulted in 89 effect sizes for the different cognitive domains all together. Since the studies included in the meta-analysis used several psychometric measures for the same domain, after closing up these, 57 effect sizes remained to work with. The direction of the effect size is shown with a + or – sign. The – sign shows poorer performance of diabetic patients in the cognitive tasks as compared with the control group. To compensate for the possible errors due to different sample sizes we computed a corrected effect size measure (D).

3. Results

Influence of diabetes on cognitive functions

Adults with diabetes showed lower performance than control subjects in all cognitive domains (Table 3). The effect sizes have the highest value on immediate verbal memory (D= -0.71), on delayed verbal memory (D= 0, 71), on psychomotor activity (D= -0.71) and overall intellectual abilities (D= -0.68). The data show little effect on general memory (D= -0.37), visual and visuo-special processing (D= -0.35), executive functions (D= -0.28), for attention / focus of (D= -0.42) and language / verbal skills (D= -0.42).

Table 3. The effect size (d) and corrected effect size (D) on the analyzed categories

Nr	Categories	Study number	Number of sizes effects on class	Total number of subjects	Effect size (d)	Corrected effect size (D)	VarD	95% confidence interval
1	Global cognitive function , IQ	3	3	224	-0.68	-0.68	0.17	[-1.15, -0.21]
2	Working memory	5	9	370	-0.08	-0.13	0.11	[-0.42, 0.17]
3	Immediate verbal memory	9	16	876	-0.85	-0.71	1.12	[-1.40, -0.02]
4	Immediate visual memory	2	2	176	-0.11	-0.11	0.01	[-0.13, -0.10]
5	Delayed verbal memory	8	15	634	-0.75	-0.71	1.10	[-1.44, 0.01]
6	Delayed visual memory	2	2	176	-0.08	-0.007	0.06	[-0.34, 0.32]

7	Memory and learning	4	5	282	-0.50	-0.37	0.21	[-0.82, 0.07]
8	Attention	7	10	712	-0.43	-0.42	0.03	[-0.55, -0.31]
9	Language	4	4	550	-0.41	-0.42	0.02	[-0.55, -0.29]
10	Visual processing	3	4	514	-0.33	-0.35	0.01	[-0.47, -0.23]
11	Psychomotor activity	3	4	514	-0.71	-0.71	0.03	[-0.93, -0.51]
12	Executive functions	7	12	712	-0.38	-0.28	0.03	[-0.41, -0.16]

On working memory category (D= -0.13), immediate visual memory (D= -0.11) and delayed visual memory (D= -0.007), the data indicate a very small effect, as well as inconsistent, the diabetes group having almost the same performances to these samples as the healthy control group.

The role of the diabetes duration and glycemic control in the impairing of cognitive processes

We calculated the predictive effect of the relation between glycemic control and cognitive functions, then the relation between diabetes duration and cognitive functions. The statistical sample between the 12 selected areas only in the case of psychomotor activity supports the hypothesis that glycemic control would be predictive on cognitive functions (R^2= 0.99, p= .02), the results being insignificant for other areas. The statistical evidence does not support the hypothesis that the diabetes duration has any effect on cognitive functions, the results being insignificant for any of the 12 cognitive domains.

4. Conclusion

Following the analysis of eligibility a number of 9 studies were included in the meta-analysis. The selection criteria was very strict, including only people aged between 18 and 65 years old; and evaluated cognitive performance using standard neuropsychological tests on normal blood glucose level. Cognitive deficits appear to be more pronounced in individuals who are more than 65 years of age, so we want to avoid the damaging effect of age on cognitive performance. But this is one of the strengths of the study too, because we wanted to exclude all other variables, which may have influenced cognition.

We proposed to determine the magnitude of cognitive dysfunctions in adults with diabetes. The present study supports the hypothesis that there is an association between diabetes and cognitive dysfunctions. Although the effect sizes of the diabetes on cognitive functions are low and moderate, it still should be considered important, because the cognitive dysfunctions can affect daily activities. In our study, we analyzed the effect of metabolic control and the diabetes duration on cognitive performance. We found that the diabetes duration was not predictive on the cognitive dysfunctions, and the metabolic control was predictive only on the psychomotor activity. The reason of this association is not absolutely clear, this assumption needs further research. It should be investigated other effects of disease variables as complications, comorbidities or other factors. The complications, however, cannot occur without a long-time inadequate glycemic control.

As any other meta-analysis this study has also its limitations. One is the relatively large number of studies which had to be excluded due the lack of sufficient data to calculate the effect size or meet the selection criteria. The main open questions that remain are the role of the different disease variables, such as the development of micro vascular complications, and the possible influence of comorbid conditions. The results of the current study support the hypothesis that there is a relationship between cognitive dysfunction and diabetes. This study was a preliminary analysis and for the future we want to analyze separately the two types of diabetes.

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